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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/630,384	07/30/2003	Robert Paul Schaudies	SAIC0062-CON1	8349

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EXAMINER	
FREDMAN, JEFFREY NORMAN	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 06/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/630,384	SCHAUDIES ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *22* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

5005

DETAILED ACTION

Special

1. It is noted that this application was granted "special" status in the petition decision of March 21, 2005. Therefore, this case is being processed out of turn early.

Claim Rejections - 35 USC § 112 – New Matter

2. Claims 16-142 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

Claims 16-142 contain several terms which appear to represent new matter.

a. The first term, found in claim 16 and many later claims, is "nonpreferential start sites". The specification was word searched using the EAST search tool and none of the words, "nonpreferential" or "start" or "site" (or any word beginning with the stem "prefer") appear within the specification. Applicant points to no basis or support in the specification for this term.

b. Similarly, the term "nonpreferential length" in claim 32 appears to represent new matter. As before, the word "nonpreferential" is not found in

the specification. The word "length" does appear several times in the specification, but virtually every time it is associated with the primer length and is not every associated with anything suggesting "amplification products having nucleotide sequences of nonpreferential length" as required by claim 32.

c. A third phrase that appears to lack support and represent new matter is "an entirety of the nucleic acid sequences", first appearing in claim 48. Only one time was a word "entirety" (or any word beginning with the stem "entir") found in the specification and that was in the incorporation by reference section. The word "entirety" was never used with reference to nucleic acid sequences. (Nor were the synonyms "complete", "whole", "full" or "total" found in the specification relating to nucleic acid sequences).

d. Fourth, the phrase in claim 104 "even if identification of the biological entity cannot be ascertained" also appears to represent new matter. A careful review of the specification failed to identify any support for this limitation and word searches for "identify" failed to find the word used in this context.

e. Fifth, in claim 107, the word "antibiotic" may represent new matter since the word does not appear in the specification. The phrase "drug resistance" does appear, but this generic term does not provide support for the species of "antibiotic".

f. Sixth, in claim 108, the word "virulence" may represent new matter since the word does not appear in the specification, nor was the concept found in a review of the specification.

g. Seventh, in claim 109, the word "transmissibility" may represent new matter since the word does not appear in the specification, nor was the concept found in a review of the specification.

In each of these cases, a careful review by the examiner of the specification failed to identify any support for these limitations. Also, no basis was identified for any of these new limitations in the response by Applicant. Since no basis has been found to support the new claim limitations in the specification, the claims are rejected as incorporating new matter.

Claim Rejections - 35 USC § 112 – Second Paragraph

3. Claims 16-47, 80-137 and 139-142 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by the term "nonpreferential" either in relation to start sites or length. The word is not defined, and indeed is not used, by the specification whatsoever. With regard to the specific phrases used, either "nonpreferential start site" or 'nonpreferential length", it is entirely indefinite what constitutes such as start site. Any primer which is used with a low annealing temperature or with nonstringent conditions, will hybridize to more sites than it's exact

complement, thereby providing "start sites" which are not the precise match of the sequence.

A contrary view is that every primer and every sequence has a specific complement and there is some relation, at least one or two terminal nucleotides, which will force a "preference" for that primer. Thus, the term "nonpreferential" in this context, without any definition from the specification or any standard definition from the art, is entirely vague and indefinite.

Claim Interpretation

4. For purposes of applying the prior art, the term "substantially an entirety" in claim 48 is extremely broad and will be interpreted using the broadest reasonable interpretation. With no specific limits, any amount of sequence amplification product is "substantially an entirety" and the application of the prior art will reflect this interpretation.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 16-23, 25-30, 32-39, 41-46, 48-55, 57-62, 64-71, 73-78, 80-87, 89-94, 96-112, 118, 119 and 121-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie et al (WO 97/22720) in view of Peng et al (J. Clin. Pathol. (1994) 47:605-608)

Beattie teaches a method for detecting at least one biological entitity in a sample (see abstract and page 53, claim 10 where Beattie claims a method of species specific identification) comprising:

(a) combining one or more nucleic acid sequences in a sample with multiple primers (see page 28, lines 12-28 and page 27, lines 5-27, for example),

(b) performing a plurality of cycles of the polymerase chain reaction to randomly amplify the sample nucleic acid sequences at each cycle of the polymerase chain reaction to produce amplification products wherein the sequences corresponding to only the sample nucleic acid sequences are the amplification products and randomly amplifying nucleic acid in the sample by a plurality of cycles of the polymerase chain reaction (see column 7, lines 30-55 or page 28, lines 1-11, for example),

(c) combining the amplification products with an array of predetermined nucleic acid sequences in predetermined locations, (page 14, lines 20-31) here, the labeled PCR products were hybridized to slide arrays (see page 17, figure 4),

(d) detecting the amplification products which have hybridized to the array and relating the nucleic acids to the biological entity in the sample (see page 43, lines 20-29).

With regard to claims 17, 25, 33, 41, 49, 57, 73, 81, 89, 97, 136-140, Beattie teaches labeling by incorporating a labelled radioactive nucleoside triphosphate (see page 32, lines 12-15).

With regard to claims 18, 34, 50, 66, 82, Beattie teaches relating the detected amplification product to a biological entity in the sample (see page 43, lines 7-19).

With regard to claims 19, 35, 51, 67, 83, 103, Beattie teaches capture probes which are 9 nucleotides in length and will vary in conservation to specific sequences(see page 34, line 16).

With regard to claim 20, 36, 52, 65, 68, 84, Beattie teaches an immobilized array and detection on the array (page 14, lines 20-31).

With regard to claim 21, 37, 53, 69, 85, Beattie teaches enzymatic detection (see page 23, lines 6-7).

With regard to claims 22-23, 38-39, 54-55, 70-71, 86-87, Beattie teaches the use of biotinylated or fluorescently labeled nucleoside triphosphates (see page 22, lines 25-30).

With regard to claims 26-27, 42-43, 58-59, 74-75, 90-91, Beattie teaches the use of porous silicon, which is silica based and opaque (see page 47, line 11, for example).

With regard to claim 28, 44, 60, 76, 92, Beattie teaches an array with predetermined positions where two or more predetermined positions characterize different biological entities (see page 26, lines 21-25, for example).

With regard to claim 29, 45, 61, 77, 93, 98-102, Beattie teaches profiling mixed populations including soil and waste treatment populations which inherently have a thousand different organisms (see page 8, lines 21-30). (see http://www.psrast.org/soilfertfact.htm, as evidence, which states "The number of different soil organism species found in one gram may be over one thousand.")

With regard to claim 30, 46, 62, 78, 94, Beattie teaches analysis of pathogens (see page 6, line 26, for example).

With regard to claims 104-106, 127-130, Beattie teaches extracting information from the genome of the biological entity which determines the species and which provides information about the biological entity, whether the species can be determined or not (see page 20, lines 1-26).

With regard to claim 107, Beattie teaches "selection of effective pharmaceutical treatment" for bacterial species, and selection of antibiotics is the basic treatment for bacterial infections (see page 2, line 25-29).

With regard to claims 108-112, Beattie teaches extraction of information on "spreading" of infectious disease, which involves virulence and transmissibility as well as treatment (see page 2, line 25 to page 3, line 5)

With regard to claims 118-119, Beattie teaches the use of conditions sufficient to achieve desired stringency (see page 13, lines 15-30).

With regard to claim 124, Beattie teaches primers in excess of six nucleotides in length (see page 31, table II, for example).

With regard to claim 141, Beattie teaches application of the method to biological warfare (see page 3, lines 2-3).

While Beattie teaches the use of arbitrary primers, Beattie does not teach the use of "randomized" primers.

Peng teaches a method to detect biological entities in samples (see abstract) comprising:

(a) combining nucleic acid sequences in a sample with multiple primers of randomized nucleotide sequence, here random hexamers (see page 605, subheading "random hexamer primer PCR"), the randomized sequences being sufficiently randomized to provide nonpreferential start sites for amplification o fthe sample nucleic acid sequences (see page 605, subheading "random hexamer primer PCR"),

(b) performing a plurality of cycles of the polymerase chain reaction to randomly amplify the sample nucleic acid sequences at each cycle of the polymerase chain

reaction to produce amplification products wherein the sequences corresponding to only the sample nucleic acid sequences are the amplification products (see page 605, subheading "random hexamer primer PCR"),

(c) analyzing the resultant PCR products (see page 606, columns 1 and 2).

With regard to claims 16, 32, 48, 78, 96, 125, 131-135, Peng teaches the use of multiple primers of randomized nucleotide sequence, here random hexamers (see page 605, subheading "random hexamer primer PCR").

With regard to claim 64, 126 and other claims, Peng teaches that nearly the entirety of the sequence will be amplified (see page 605, column 2).

With regard to claims 121-123, Peng teaches primers that are six nucleotides in length (see page 605).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the predetermined arrays of Beattie with the RP-PCR method of Peng since Peng states "The main advantage of RP-PCR over other methods such as the random 15mer and linker adaptor methods for PCR random amplification of genomic DNA is that the random hexamer primers are inexpensive and readily available. RP-PCR, together with some newly developed techniques such as microdissection, should make it feasible to perform multiple genetic analyses on defined cell populations on tissue sections or scanty amounts of pathological material (see page 607, column 2)". This motivation is directly applicable to Beattie, who uses a random 15mer type method since Beattie is expressly interested in "(1) greater speed of

analysis; (2) higher throughput of analysis (ability to process larger numbers of samples per work day); (3) lower cost per analysis; (4) greater statistical reliability due to much higher information content (see page 7,lines 2-5)." Therefore, an ordinary practitioner, interested in reducing cost and performing analysis a small sample amounts with high throughput would have been motivated to use the RP-PCR method of Peng as the amplification method in the predetermined array method of Beattie in order to achieve the benefits desired by Peng and Beattie of performing "multiple genetic analyses on defined cell populations (see Peng, page 607, column 2)" at improved speed, throughput, cost and statistical accuracy.

8. Claims 24, 40, 56, 72 and 88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie et al (WO 97/22720) in view of Peng et al (J. Clin. Pathol. (1994) 47:605-608) and further in view of Cronin et al (U.S. Patent 6,207,880) and further in view of Boeringer-Manheim catalog (1998) pages 70-76).

Beattie in view of Peng teach the limitations of claims 16-23, 25-30, 32-39, 41-46, 48-55, 57-62, 64-71, 73-78, 80-87, 89-94, 96-112, 118, 119 and 121-141 as discussed above. Beattie in view of Peng do not teach the use of digoxigenin.

Boeringher-Manheim catalog (1998) teaches labeling by incorporation using radioactive, fluorescent, and digoxigenin labels and teaches enzymatic detection with NBT and BCIP.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the labeling method of the Boeringer-Manheim

catalog in the method of Beattie in view of Peng since the catalog states that the labeling method uis used for rapid random primed labeling of DNA (page 70) and that "This convenient 'all in one' principle of High Primer reduces pipetting steps to a minimum and increases accuracy and reproducibility of labeling reactions (page 70)". An ordinary practitioner would have been motivated to utilize the method of Boeringer-Manheim with the amplification and detection method of Beattie in view of Peng in order to improve accuracy and reproducibility while rapidly labeling the nucleic acid of interest.

9. Claims 31, 47, 63, 79, 95, 113-117 and 142 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beattie et al (WO 97/22720) in view of Peng et al (J. Clin. Pathol. (1994) 47:605-608) and further in view of Cronin et al (U.S. Patent 6,027,880).

Beattie in view of Peng teach the limitations of claims 16-23, 25-30, 32-39, 41-46, 48-55, 57-62, 64-71, 73-78, 80-87, 89-94, 96-112, 118, 119 and 121-141 as discussed above. Beattie in view of Peng do not teach oligonucleotides longer than 30 nucleotides in length, specific hybridization conditions or tiled or redundant arrays.

Cronin teaches detection of a variety of targets including anthrax (see column 9, line 59) using a microarray with tiled or overlapping sequences (see column 10, lines 43-67 and column 11, lines 1-57). Cronin teaches probes that are more than 30 bases in length (see column 12, lines 38-40, where probes may have 50, 75, 90 or 99 nucleotides in common with the target). Cronin specifically teaches block tiling, which is one of several tiling strategies taught by Cronin that will result in redundant, overlapping

probes on the array of a single biological entity which are subsequences of one another (see column 21, line 56 to column 22, line 67 for one example of the tiling strategies).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the array type of Cronin in the method of Beattie in view of Peng since Cronin teaches "The relative specific binding of probes in the second group indicates whether the target sequence is the same or different from the second reference sequence. Such methods are particularly useful for analyzing heterologous alleles of a gene. Some methods entail hybridizing both a reference sequence and a target sequence to any of the arrays of probes described above. Comparison of the relative specific binding of the probes to the reference and target sequences indicates whether the target sequence is the same or different from the reference sequence. (see column 5, lines 58-67)." An ordinary practitioner, recognizing that Beattie is interested in comparing a target and reference sequence in order to identify microorganisms, and taught by Cronin that the tiling array is a useful method to compare binding of organisms including Anthrax, would have been motivated to use the tiling array since it provides "a high degree of confidence in the sequence output (see column 9, line 9)." With regard to the fact that Beattie prefers shorter arrays, Beattie recognizes that the length of the probes are target dependent (see page 10).

With regard to the specific hybridization conditions, an ordinary practitioner would have recognized that the results optimizable variable of hybridization temperature could be adjusted to maximize the desired results. Beattie expressly teaches that the

hybridization conditions depend on the sequence length (see page 10). As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific hybridization temperature was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Response to Declaration

10. The Declaration under 37 CFR 1.132 filed July 30, 2003 is insufficient to overcome the rejection of the claims based upon 35 U.S.C. 103 as set forth in the last Office action because: The Declaration is an attempt to demonstrate that there is a "long felt need" for the invention. The specific need identified by the Declaration is "The need for a broad spectrum, high confidence biological detection and identification svstem has existed for over 50 years (see page 2 of the declaration)." While the Declaration shows that there is a need, the Declaration also states "By 1991, although scientists recognized the need to develop biological warfare detection methods, the only proposed solution was to use available laboratory technologies on massive scales. (see page 4 of the declaration)."

The MPEP notes at 716.04 that "Second, the long-felt need must not have been satisfied by another before the invention by applicant." In this case, the declaration itself provides express evidence that there was a solution to the "long felt need" and that this need was satisfied by available laboratory technologies. As the Federal Circuit noted in *Newell Companies v. Kenney Mfg. Co.*, 864 F.2d 757, 768, 9 USPQ2d 1417, 1426 (Fed. Cir. 1988) "[O]nce another supplied the key element, there was no long-felt need or, indeed, a problem to be solved". Here, available laboratory techniques are expressly stated by the Declarant as being able to satisfy the need. This is evident because in every specific instance cited by the Declarant, whether the Anthrax attacks in 2001 or the investigations of hoaxes by the FBI, available laboratory techniques were and are used to determine whether a biological warfare agent was present or not. There was no inability to detect these agents which is awaiting Applicant's invention.

Therefore, the Declaration regarding long felt need is not found persuasive to demonstrate a secondary consideration necessary to overcome an obviousness type rejection.

Response to Arguments

11. Applicant's arguments filed November 1, 2004 have been fully considered but they are not persuasive.

Most of Applicant's arguments are moot since the grounds of rejection is different than the ground argued. Applicant does argue that Beattie does not teach hybridization to predetermined oligonucleotides on an array. This is simply incorrect. Beattie clearly teaches hybridization to such an array (see figure 1).

With regard to the argument of long felt need, this secondary consideration relates to the situation where there is no solution to the problem posed. In this case, standard laboratory techniques clearly are available and are capable of resolving whether a specific sample warrants concern as a bioterror agent. There is no long felt need solely to detect bioterror or other agents (most claims not being limited to bioterror agents).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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1/07/K